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Metabolism of Trichloroethylene and Tetrachloroethylene in Human Subjects

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A linear correlation exists between the trichloroethylene concentration in the work environments and the level of total trichloro compounds in the urine of the workers, as expressed by the equation: $Y = 7.25 \equiv \chi + 5.5$, where Y is trichloroethylene in air (ppm) and X is total trichloro compounds in urine (mg/l.). Trichloroethanol level is also linearly related to trichloroethylene concentration, while trichloroacetic acid level deviates from the linear relation when trichloroethylene level exceeds 50 ppm.

In the case of tetrachloroethylene exposure, both trichloroethanol and trichloroacetic acid levels, and consequently the total trichloro compound level, reach a plateau at tetrachloroethylene level well below 100 ppm.

The mean urinary biological half-life is 41 hr for trichloroethylene and 144 hr for tetrachloroethylene. The two values are the largest of the values so far obtained with organic solvents. The respiratory half-life is shorter than the urinary half-life, both in trichloroethylene and in tetrachloroethylene.

Applications of the urinalyses in clinical cases are described. In one case of trichloroethylene dependency, a longer urinary half-life of 73 hr was observed.

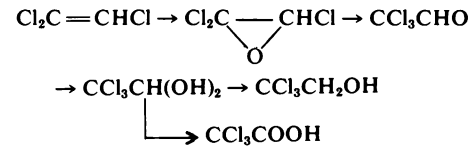
An automated system is presented for the determination of total trichloro compounds in human urine. The system can analyze the samples at the rate of 20 samples per hour with an accuracy comparable to that of the time-consuming manual analysis.

Trichloroethylene and tetrachloroethylene have been widely used in industries as solvents, particularly in degreasing of metals, plastics, and cloth (*1*). Accordingly, the metabolism and toxicity of these chemicals has been extensively studied (*2–8*). A recent report on carcinogenicity of trichloroethylene in mice (*9*) called attention to the toxicology of these popular solvents in relation with vinyl chloride and vinylidene chloride. Among the basic information requested are the applicability of urinalysis for the metabolites to detect exposure of humans to these solvents and quantitative analysis in accumulation in and excretion from bodies of those occupationally exposed to these compounds.

It is the purpose of the present communication to summarize in brief the results given in our previous publications on the subjects (*10–16*). A quantitative relationship is reported between the vapor concentrations of the two chemicals in the workroom air and the metabolite concentrations in the urine of the workers. The urinary biological half-life of trichloroethylene and tetrachloroethylene metabolites was also studied in persons occupationally exposed to the vapor under various conditions. In addition, an automated system for the determination of total trichloro compounds in human urine is presented which should facilitate a wider application of biological monitoring to prevent possible adverse effects on health.

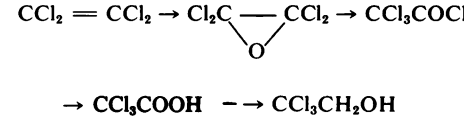
The main metabolic pathways for trichloroethylene and tetrachloroethylene are summarized in Eqs. (1) and (2).

Metabolism of trichloroethylene:



(1)

Metabolism of tetrachloroethylene:



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Materials and Methods

Employees and Their Workshops

To establish a quantitative relation between environmental vapor concentrations and urinary metabolite levels, 10 trichloroethylene workshops employing 51 male workers and 7 tetrachloroethylene workshops with 34 male workers were selected, in which machines (mostly degreasers) were run automatically and continuously while the locations of the workers were fixed in closed and relatively small workrooms so that the vapor was evenly distributed throughout the room at a relatively constant level.

The biological half-life study was carried out in 30 workers (24 males and 6 females) in five trichloroethylene workshops and 13 workers (9 males and 4 females) in two tetrachloroethylene workshops.

Urine Samples

For the balance study, surveys were carried out in the latter half of weeks. Urine samples were collected at about 3:00 PM after urine was passed at about 1:00 PM. Samples with a specific gravity less than 1.010 were discarded. In the case of biological half-life determination, urine was sampled around 8:00 AM on Saturday, Sunday (i.e., nonexposure days) and again on Monday before the beginning of work. The samples were subjected to metabolite analysis. Determination of total trichloro compounds (TTC), trichloroethanol (TCE), and trichloroacetic acid (TCA) was carried out after Tanaka and Ikeda (*17*) as depicted in Figure 1. In some instances, a time-saving version (*18*) was also employed. The method was further automated as described below.

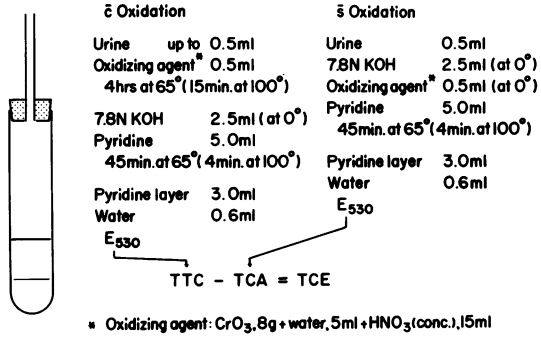

FIGURE 1. Determination of TTC, TCE, and TCA by the manual method.

Determination of Trichloroethylene and Tetrachloroethylene in Air

The vapor concentration was measured by use of Kitagawa detection tubes (*19*). At least five determinations were made at various sites in each workshop and the average was taken to represent the environment. The maximum and minimum values differed from the mean by less than 30% of the mean.

Statistical Analysis

An assumption was made that a lognormal distribution would be applicable (*20*) to urinary metabolite concentrations. Regression lines were calculated with weighting for the numbers of samples (*21*).

Results and Discussion

Quantitative Relationship between Vapor and Metabolites

Results from the workshop survey and urinalysis are summarized in Figures 2 and 4. When geometric means (of 4 to 9 samples each) of metabolite levels were plotted against trichloroethylene concentration (Fig. 2), it was found that the relationship for TCE appears to be well represented by a straight regression line (Fig. 2, middle), while the relationship in the case of TCA concentration (Fig. 2, bottom) apparently deviates from the straight line when the vapor concentration exceeds 50 ppm. As the share of TCA is much smaller than that of TCE, the levels of TTC (or the sum of TCE and TCA) in the urine are linearly related to the ambient trichloroethylene concentration (Fig. 2, top), the regression line being defined by Eq. (3):

$$Y = 7.25X + 5.5 \qquad (3)$$

where Y is TTC in urine (mg/l.) and X is trichloroethylene in air (ppm).

It should be noted that essentially no Fujiwara reaction-positive compound is detected in the urine of the nonexposed subjects (*22*), and therefore, the regression line as well as SD range lines converges at the origin.

Based on Eq. (3), it is possible to calculate the amount of trichloroethylene excreted into urine in the form of the metabolites after the exposure at a given concentration. At 50 ppm (268 mg/m^3), the estimated amount of trichloroethylene to be excreted into urine is about 368 mg/l. (as TTC) or 20–30 mg/hr (as trichloroethylene) when the rate of

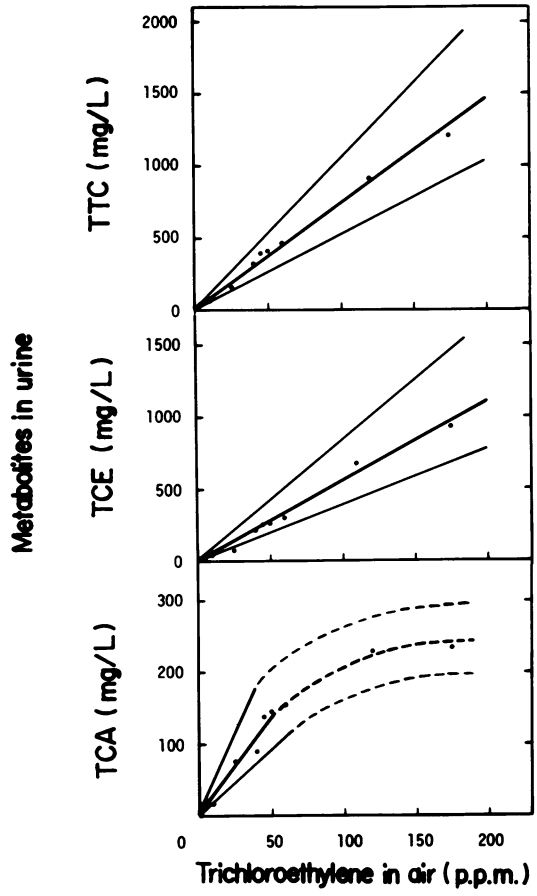

FIGURE 2. Relation between atmospheric concentration of trichloroethylene and metabolite concentration in urine. Lines are means and SD ranges. Each symbol represents an average of 4 to 9 samples.

urine excretion is assumed to be 50–100 ml/hr. The amount of trichloroethylene absorbed through the lungs may be calculated to be about 80 mg/hr with the two assumptions that the lung up-take efficiency is about 50% [35-63% cited in the literature (*7, 23*)] and that the respiratory volume under the working condition is about 10 l./min:

$$268\ (\text{mg/m}^3) \times 10\ (\text{l./min}) \times 60\ (\text{min}) \times (50/100) = 80\ \text{mg/hr}.$$

Such being the case, only one third of the absorbed trichloroethylene is excreted into urine during the work period, although a part of trichloroethylene retained may also be exhaled into alveolar breath (*7*). The present observation is in a good agreement with a long biological half-life as to be described later. In connection with the results given in Figure 2, it is noteworthy that the level of urinary metabolites measured as TTC is also linearly related to the methyl chloroform concentration in the workroom air (Fig. 3), although methyl chloroform is known to be primarily exhaled unchanged into alveolar breath (*24*), and excretion into urine as metabolites is only a minor route of elimination (*24*).

Once such a relation as shown in Figure 2 (top) and Figure 3 is established, a lower fiducial limit at a given probability at a given vapor concentration can be utilized as a screening level for the biological monitoring (*14*). The degree of risk of error permitted may vary depending on the purpose of the screening test, and it is of practical importance to make clear the percentage risk of misjudgement. The use of the lower fiducial limit ($p = 0.10$) as a screening level will result in underestimation of exposure at 5%, while the actual exposure of about half the workers will be underestimated when the screening level is set at the mean.

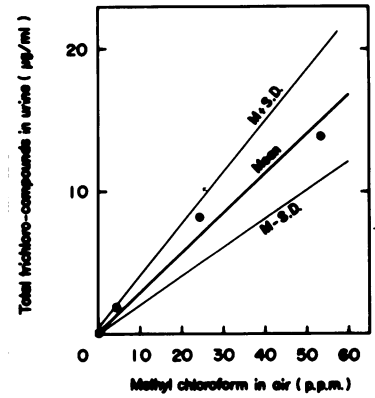

FIGURE 3. Relation between atmospheric concentration of methyl chloroform and metabolite concentration in urine. Lines are means and SD ranges. Each symbol represents an average of 10 to 26 samples. From Seki et al. (*15*).

The mean metabolite concentrations at 10 ppm and 50 ppm [the latter being current Japanese TLV for 1976 (*26*)] are depicted together with fiducial ranges ($p = 0.10$) in Table 1. Taking the lower fiducial range, the screening level at 5% risk at 50 ppm will be 292 mg/l. and 58 mg/l. at 10 ppm. The screening level at these exposure intensity is several decades higher than the maximum of the nonexposed level, indicating that the workers at these exposure intensities can be clearly separated from the nonexposed.

Table 1. Total trichloro compound levels in urine after trichloroethylene exposure.

Exposure level, ppm	Mean, mg/l.	Fiducial ranges ($p = 0.10$), mg/l.
0	0–0.9[a]	
10	84	58–122
50	421	292–608

[a]Minimum–maximum values observed.

A linear regression line does not hold in the case of tetrachloroethylene exposure. Despite wide variations in urinary metabolite levels, it is clear that both TCE (Fig. 4, middle) and TCA (Fig. 4, bottom) levels, and consequently TTC level (Fig. 4, top) reach a plateau at concentrations well below 100 ppm tetrachloroethylene. It should also be noted that the metabolite concentration at an equal exposure intensity below 50 ppm of tetrachloroethylene is about one fifth of that of trichloroethylene. Such observations suggest that the capacity of humans to metabolize tetrachloroethylene is rather limited even at fairly low concentrations. The relative nonsusceptibility of tetrachloroethylene to biotransformation has been suggested also by others. Sjöberg (*27*) demonstrated that trichloroethylene is more readily oxidized than tetrachloroethylene when brought into contact with heated iron. To judge from the amount of phosgene formed, trichloroethylene is about 10 times as susceptible to oxidation as tetrachloroethylene. Byington and Leibman (*6*) isolated chloral hydrate rather than trichloroethylene epoxide as the first stable intermediate in *in vivo* trichloroethylene oxidation experiment, and trials by others (*28*) were also unsuccessful in isolating the oxide due to its instability, while tetrachloroethylene oxide was isolated by vacuum-distillation (*29*).

Biological Half-Life of Trichloroethylene and Tetrachloroethylene

The results from urinary biological half-life study are summarized in Table 2. Among the trichloroethylene-exposed workers, the half-life values for TTC are not uniform. No relation, however, was observed as to exposure conditions or sex. A number-weighted mean for TTC half-life was about 41 hr, which is essentially the same as the values calculated from the data given by various authors (*4, 7, 23, 30*) who studied human volunteers with no history of occupational exposure, indicating that the occupational exposure to trichloroethylene may not modify the urinary biological half-life. Compared with TCE, TCA had a longer biological half-life (Table 2), as reported by Bartoníček (*4*).

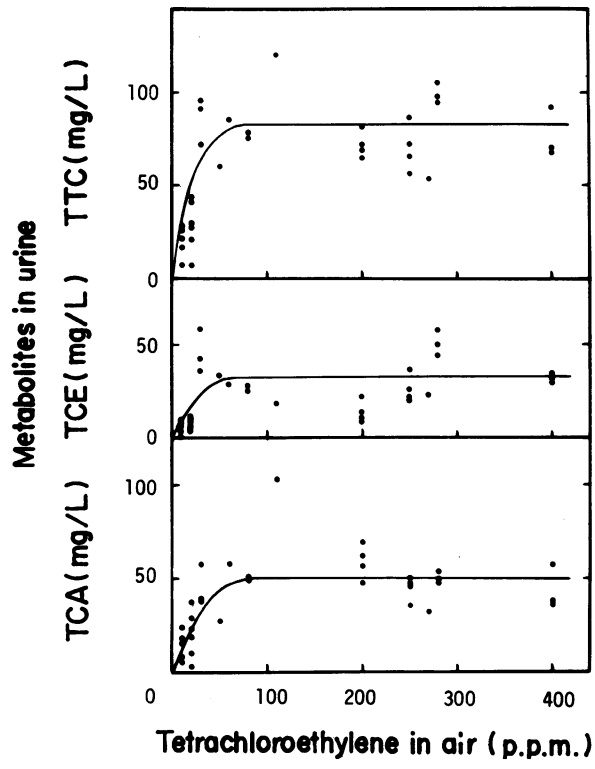

FIGURE 4. Relation between atmospheric concentration of tetrachloroethylene and metabolite concentration in urine. Curves were drawn by eye.

Table 2. Biological half-life of metabolites in the urine of the workers occupationally exposed to trichloroethylene or tetrachloroethylene.

Compound	Groups	Biological half-life, hr		
		TTC	TCE	TCA
Trichloroethylene	A (6 males)[a]	42.7 ± 4.5		
	B (6 males)[b]	48.8 ± 11.7		
	C (6 males)[c]	26.1 ± 4.8	15.3 ± 2.2	39.7 ± 8.7
	D (6 males)[d]	33.7 ± 6.8		
	E (6 females)[e]	50.7 ± 7.7	42.7 ± 9.1	57.6 ± 19.8
Tetrachloroethylene	F (6 males)[f]	123.3 ± 23.5		
	G (6 females)[g]	190.1 ± 32.9		

[a]Exposure: 10—150 ppm, 4 hr once or twice a month.
[b]Exposure: 5—170 ppm, 2 hr once or twice a month.
[c]Intermittent exposure to 200 ppm during 8 hr/day work.
[d]Exposure: 20–40 ppm, 8 hr day, 5 days/week.
[e]Intermittent exposure to 50 ppm during 8 hr/day work.
[f]Exposure: 30–100 ppm, 8 hr/day, 5 days/week.
[g]Exposure: 10–20 ppm, 8 hr/day, 5 days/week.

The half-life of urinary metabolite after tetrachloroethylene exposure was between 100 and 200 hr, much longer than that of trichloroethylene. The apparent difference between the sexes is considered yet to be confirmed. The urine samples obtained for three consecutive days would show only 20% reduction in metabolite concentration, as the half-life is as long as 6 days. The small decrease will inevitably reduce the accuracy of the measurement under the conditions employed. The best estimate of the half-life obtained as a number-weighted mean is 144 hr.

The half-life of trichloroethylene and tetrachloroethylene as expired into alveolar breath could be calculated from the data of the twin experiments of volunteer exposures carried out by Stewart et al. (*7, 8*), and these values were compared with urinary half-life (Table 3). The urinary values are longer than the respiratory values. It is worthy of note that the ratio of the half-life of trichloroethylene to that of tetrachloroethylene is about 1:3 regardless of the routes of elimination. On the basis of the equation given by Roach (*31*), one can estimate that tetrachloroethylene will accumulate in the body at about 3 to 4 times the rate of trichloroethylene under the same conditions of repeated exposures. The urinary biological half-life for trichloroethylene and tetrachloroethylene, 41 hr and 144 hr, respectively, appear to be the longest among the values for organic solvents. The counterpart values for three aromatics, toluene, xylene and styrene are about 7 (*32*), 7 (*32*), and 8 hr (*33*), respectively, and the values for phenol and catechol are even shorter (*34, 35*).

Table 3. Respiratory and urinary biological half-life of trichloroethylene and tetrachloroethylene.

	Half-life, hr		
Excretion	Trichloroethylene	Tetrachloroethylene	Ratio
Respiratory[a]	25	65	1 : 2.6
Urinary[b]	41	144	1 : 3.5

[a]Calculated from the data of Stewart (7, 8).
[b]Number-weighted mean of the values in Table 1.

Trichloroethylene Half-Life in Clinical Cases

A urinary half-life of over 70 hr was observed in a patient addicted to trichloroethylene (*10*), the value being almost twice as long as that of ordinary factory workers (Fig. 5). The patient was a 38 year-old male who had a habit of sniffing a cloth soaked in trichloroethylene up to three times a day. He was admitted to a hospital with suspected volvulus, where he developed disorientation, visual hallucinations, delusions of persecution, and other psychiatric symptoms after hospitalization for 2 days. The disappearance of the trichloroethylene metabolites was rather slow. The half-life was calculated to be 73 hr for TTC and 48 for TCE. The value for TCA was essentially the same with that for TTC. The role of the long biological half-life in the etiology of trichloroethylene dependency remains, however, yet to be elucidated.

After an accidental short-term exposure to an anesthetic concentration of trichloroethylene vapor, a 20 year-old girl showed complete loss of sensation in the trunk and the lower extremities when she recovered from unconsciousness (*13*). Urine samples obtained on days 21 to 25 after the accident contained up 32 mg/l. of TTC. Assuming that the urinary biological half-life for TTC is 41 hr as described above, the level of TTC in the urine right after the accident could be as high as 10 g/l., which corresponds to an environmental trichoroethylene concentration of several thousand ppm (Fig. 2), a level regarded as narcotic (*1*). The etiology of the transverse lesion found in the spinal cord remained unknown.

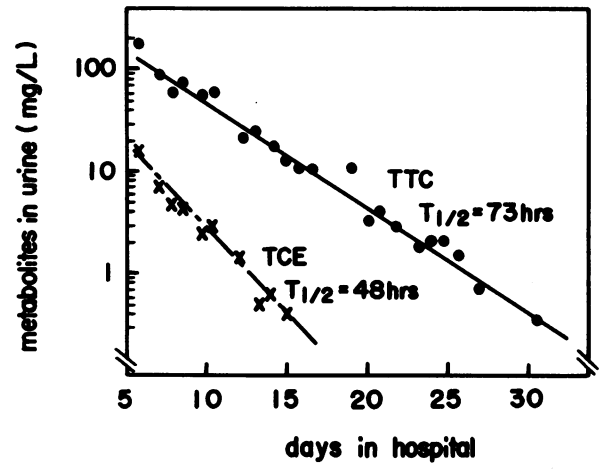

FIGURE 5. Decrease in metabolite levels in the urine of a patient addicted to trichloroethylene.

Automated System for Determination of TTC in Human Urine

Although the significance of urinary TTC determination is well established as an index of the exposure, complexity of the manual analysis often limits a wider application of biological monitoring. Attempts were made to develop an automated system for TTC urinalysis with an accuracy at least comparable to that of the manual analysis. The re-

sult is shown in Figure 6 as a flow diagram utilizing Technicon AutoAnalyzer components (*16*). The principle employed was essentially that of the time-saving version (*18*) of the original method (*17*). Urine samples were picked up at a rate of 20 samples per hour, mixed with an oxidizing reagent (composed of chromium trioxide and nitric acid), preheated, and subjected to oxidation at 96°C for 15 min. The digest was made alkaline, mixed with pyridine, and heated at 85°C for Fujiwara reaction. The colored organic phase was separated and clarified with water, and the extinction at 550 nm was measured and recorded. In order to evaluate the accuracy of the automated analysis, urine samples were collected from 54 workers exposed to trichloroethylene and analyzed for TTC by both manual and automated methods. The results shown in Figure 7 indicate that a close relation exists between the two results. The regression line has a slope of essentially 1, and the intercepts at the two axes are essentially zero, while the correlation coefficient r is 0.989.

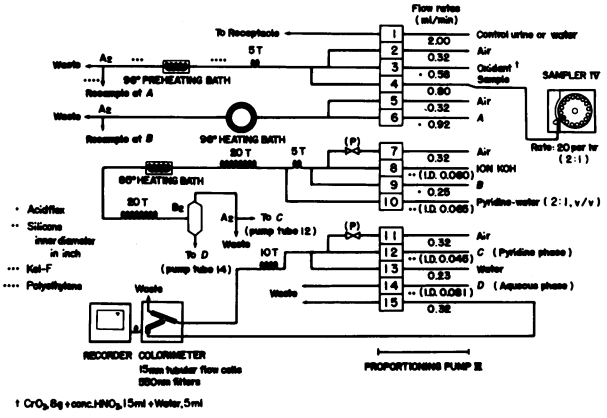

FIGURE 6. Flow diagram for automated TTC determination.

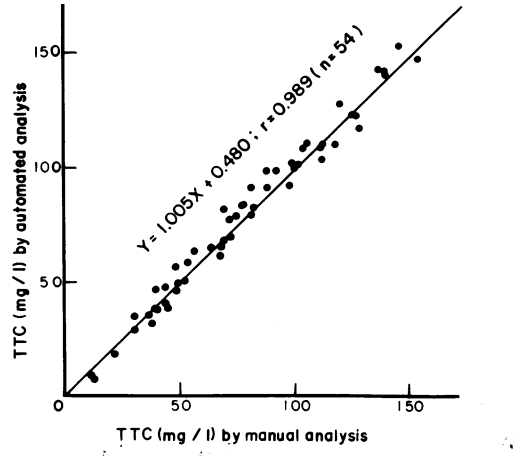

FIGURE 7. Correlation between results from manual and automated analyses.

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